REMARKS

Claims 74-76 are currently pending in this application. Claim 74-76 have been amended and support can be found in the claims and specification as originally filed.

With respect to all claim amendments, Applicants have not dedicated, disclaimed, or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Nonstatutory obvious-type double patenting rejection

Claims 74-76 have been rejected under the judicially created doctrine of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1, 39, and 40 of U.S. Patent No. 5,723,286. A Terminal Disclaimer over U.S. Patent 5,723,286 is submitted with this response. Applicants request its entry and the withdrawal of the rejection.

Rejection under 35 U.S.C. §112, first paragraph - Enablement

Claims 74-76 have been rejected under 35 U.S.C. §112, first paragraph allegedly because the "specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims" (page 4 of the January 15, 2008 Office Action).

Without acquiescing to the Examiner's rejection and solely in the interest of expediting prosecution in this case, the currently pending claims have been amended to recite "a polynucleotide sequence that encodes a fusion protein comprising a peptide fused to a pIII coat protein of a filamentous bacteriophage so that the N-terminal amino acid of said fusion protein is the N-terminal amino acid of said peptide."

The Examiner asserts that the instant specification "does not reasonably provide enablement for (1) any other size peptide; (2) fusion protein with unprocessed coated protein" (*Id.*). Applicants respectfully disagree and submit that the instant specification enables the scope of the currently amended claims and the Applicants' invention is not limited to hexapeptides or fusion proteins with unprocessed coat protein.

A. The Legal Standard

According to M.P.E.P.§2164.05(a),

> The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ 2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).
> (Emphasis added)

The Federal Circuit has held that "[t]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997). Nonetheless, enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly excessive." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

As discussed below, Applicants submit that one of ordinary skill in the art would be able to make and use the invention without undue experimentation. An allegation of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re* Wands factors). These factors include: "(1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988). In addition, according to MPEP §2164.06, the mere fact that an extended period of experimentation is necessary does not make such experimentation undue (*In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977)). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the

experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed (*Enzo Biochem., Inc. v. Calgene, Inc.,* 188 F.3d 1362 (Fed. Cir. 1999), at 1372 (quoting *In re* Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991)).

B. Application of the Legal Standard

As currently amended, claims 74-76 recite "a polynucleotide sequence that encodes a fusion protein comprising a peptide fused to a pIII coat protein of a filamentous bacteriophage so that the N-terminal amino acid of said fusion protein is the N-terminal amino acid of said peptide." Applicants submit that the full scope of the claims, as currently amended, is enabled.

1. Peptides

Applicants respectfully submit that the present specification provides sufficient detail to enable those of ordinary skill in the art to practice the full scope of "peptide" as currently claimed because (i) the use of various sized peptides in phage display libraries is well-known to those of ordinary skill in the art; and (ii) the instant specification provides detailed protocols for creating libraries based on different sized peptides.

The use of different sized peptides for generating phage display peptide libraries has been demonstrated by those of ordinary skill in the art. For instance, Malik *et al.*, cited by the Examiner states that for the display of peptides on pIII, "there appears to be little restriction on the size of the insert" [emphasis added] (page 10, 1st column, 2nd paragraph). In addition, Gho *et al.* (1997) Cancer Research. 57, 3733-3740 reported the construction of an octapeptide library in which the peptide epitopes were fused to the N-terminus of pIII coat protein in M13 phage (page 3733, 2nd paragraph of right column). This publication cites reference 39, a report listing authors Cwirla, Dower, and Barrett, who are also the inventors of the present application. As such, Applicants respectfully submit that Gho *et al.* successfully implemented a strategy that is similar to that used by the Applicants in the present invention to create an octapeptide library.

The instant specification provides step-by-step guidelines and protocols for the creation of libraries with different sizes of peptides. For instance, the specification describes how to design the oligonucleotides that contain the variable regions of the library members. The specification states that to:

> generate the collection of oligonucleotides which forms a series of codons encoding a random collection of amino acids and which is ultimately cloned into the vector, a codon motif is used, such as $(NNK)_x$, where N may be A, C, G, or T (nominally equimolar), K is G or T (nominally equimolar), and x is typically up to about 5, 6, 7, or 8 or more, thereby producing libraries of penta-, hexa-, hepta-, and octa-peptides or more. [page 7 line 33 to page 8, line 6]

In addition, the specification also describes how to add additional amino acids to a peptide or peptides found to be active (page 10 line 26 to page 11 line 9). As demonstrated in Example 1, an appropriate filamentous bacteriophage vector with suitable cloning sites can be constructed by cloning an oligonucleotide of choice to place a variable peptide region at the N-terminus of a bacteriophage coat protein. The vector-containing the variable oligonucleotide is then transformed into a bacterial host, phage are isolated and selected based on binding to a preselected molecule. There is no indication that the protocols provided by the Applicants would not allow a person of ordinary skill in the art to construct and analyze a library containing peptides other than hexapeptides. Accordingly, the present specification need not disclose any specific examples of a library containing peptides other than hexapeptides.

Applying the *In re Wands* factors to the present claims, we find that:

1) The nature of the invention:

The nature of the invention is a novel method for identifying peptides which bind to a preselected molecule.

2) The breadth of the claims:

The claims are directed to a method of identifying a polynucleotide sequence that encodes a peptide which binds to a preselected receptor molecule, comprising: transforming host cells by electroporation with at least 10^8 different filamentous bacteriophage expression vectors,

wherein each of said different vectors comprises a polynucleotide sequence that encodes a fusion protein comprising a peptide fused to a pIII coat protein of a filamentous bacteriophage so that the N-terminal amino acid of said fusion protein is the N-terminal amino acid of said peptide, and wherein said different vectors are constructed by ligating each polynucleotide of a mixture of at least 10^8 different polynucleotides to a bacteriophage cloning vector that encodes the coat protein so as to form a coding sequence for said fusion protein, wherein each of said different polynucleotides comprises a series of codons encoding a random collection of amino acids and encodes a different peptide; followed by cultivating, selecting, and sequencing steps. A person of ordinary skill in the art would appreciate that libraries containing peptides, other than hexapeptides, could be routinely constructed, as evidenced by the publications of Malik *et al.* and Gho *et al.* In addition, the claims are limited in scope to peptides fused to a pIII coat protein of a filamentous bacteriophage so that the N-terminal amino acid is the N-terminal amino acid of the peptide. As such, the claims are not broad in that the subject matter is explicitly recited in the claims.

3) The presence or absence of working examples:

As previously discussed, the specification provides a working example of how to make and analyze libraries containing peptides of different sizes. Such an example would allow a person of ordinary skill in the art to practice the present invention without undue experimentation.

4) The state of the prior art / the predictability or unpredictability of the art:

The Examiner argues that Malik *et al.* "teach a high level of unpredictability in the size of peptides displayed on the pVIII coat protein of filamentous bacteriophage", concluding that this allegedly "high level of unpredictability regarding the size of the display peptide ... combined with the limited guidance in the specification is Applicants' invitation to undue and unpredictable experimentation to further test ... different size peptides" (page 6 of the January 15, 2008 Office Action).

Applicants respectfully disagree and submit that the predictability of biotechnological arts is generally high with regard to the creation of libraries displaying different sized peptides

on pIII coat proteins, as evidenced by the above discussion of both Malik *et al.* and Gho *et al.* As such, the level of predictability that libraries of different sized peptides could be routinely created and analyzed by those of ordinary skill in the art is high.

5) The amount of direction or guidance provided:

The instant specification provides sufficient direction and guidance to enable the invention as presently claimed. As discussed above, the specification provides step-by-step guidelines and protocols for the creation of libraries with different sizes of peptides. Applicants respectfully submit that based on these disclosures, one skilled in the art could easily create and analyze a library containing peptides other than hexapeptides. As such, the specification provides sufficient guidance to a person of ordinary skill in the art to practice the present invention.

6) The relative skill of those in the art:

The relative skill of those in the art is high, one of ordinary skill in the art often having an advanced academic degree and several years of relevant experience.

7) The quantity of experimentation necessary:

As discussed above, the use of different sized peptides for generating phage display peptide libraries has been demonstrated by those of ordinary skill in the art. Given the disclosure of suitable methods in the present specification, it is believed that no undue amount of experimentation is required to practice the invention as presently claimed. The construction and analysis of a library containing peptides other than hexapeptides as contemplated by the currently pending claims would require no more than routine experimentation.

Thus, in view of the above, since the specification describes in sufficient detail methods for making and analyzing peptide libraries; since the nature of the invention, state of the prior art, and relative skill in the art allow one of ordinary skill in the art to follow these teachings; since the predictability of biotechnological arts is generally high regarding the creation and analysis of peptide libraries as contemplated by the present invention; since the claims are not broad in that the subject matter claimed is explicitly recited in the claims, Applicants submit that the quantity of experimentation needed to practice the invention is not undue and that the specification

enables one of ordinary skill in the art to make and use the invention to the full scope of the claims. Therefore, Applicants submit that the claims as currently amended meet the enablement requirement under 35 U.S.C. §112. Applicants request that the Examiner withdraw the rejection.

2. Coat protein

Applicants respectfully submit that the present specification provides sufficient detail to enable those of ordinary skill in the art to practice the full scope of "coat protein" as currently claimed. For example, the specification states

> In preferred embodiments, where phage proteins are initially expressed as preproteins and then processed by the host cell to a mature protein, the library members are inserted so as to leave the peptide encoded thereby at the N-terminus of the mature phage protein after processing or a protein substantially homologous thereto. (emphasis added) [page 3, lines 15-20]
>
> [and]
>
> The coat protein is typically expressed as a preprotein, having a leader sequence. Thus, desirably the oligonucleotide library is inserted so that the N-terminus of the processed bacteriophage outer protein is the first residue of the peptide ... (emphasis added) [page 7, lines 5-9]

Therefore, the specification clearly describes that upon transformation of a vector encoding a fusion protein with a coat protein, the host cell mechanisms can be relied upon to process the pIII preprotein, if necessary, for assembly into the intact phage particle.

In addition, the specification also indicates that the use of an unprocessed coat protein does not interfere with the display of a peptide on the surface of a phage particle. Example 1 describes the construction of a diverse oligonucleotide library where reconstruction of the amino acid sequence is in the vicinity of the signal peptidase site (page 18, lines 13-15). The specification does indicate that library construction "necessarily alters amino acids in the vicinity of the signal peptidase cleavage site" and processing inefficiencies have been reported for the pVIII coat protein (page 23, lines 41-46). However, this issue does not apply to the Applicants' invention. As shown in Table 2 of the specification, the ratios for the observed occurrence of each amino acid range from about 0.5 to 2, which is consistent with a random distribution of sequences (see also page 23, lines 36-39). The specification then states that were pIII coat

proteins to exhibit the same problems as pVIII coat proteins,

> the diversity of peptides contained in the library would be reduced ... [and t]he finding that most amino acids appear at each position of the variable peptides of randomly selected phage indicates that processing defects do not impose severe constraints on the diversity of the library. (emphasis added) [page 23 line 46 to page 24 line 2]

Based upon the foregoing, Applicants submit that the fusion of a foreign peptide to an unprocessed pIII coat protein would not "interfere with the assembly of the phage particle and the display of the peptide on the surface of the phage particle" as argued by the Examiner on page 5 of the Office Action. As such, the present invention is not limited to "processed pIII". Therefore, Applicants submit that the claims as currently amended meet the enablement requirement under 35 U.S.C. §112. Applicants request that the Examiner withdraw the rejection.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. 07-1700 (referencing Attorney's Docket No. **AFX-0001 US C7 (123886-181973)**).

Respectfully submitted,

Date: June 16, 2008

By: _____
Jeffery P. Bernhardt (Reg. No. 54,997)

GOODWIN PROCTER LLP
135 Commonwealth Drive
Menlo Park, CA 94025
Telephone: 650 752-3106
Customer No. 77845

LIBC/3317954.1